

New and Notable

Starting from the Ground State Up: Factors Influencing Synaptic Plasticity

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To many, long-term potentiation (LTP) and long-term depression (LTD) represent two forms of synaptic plasticity that play an obligate role in the encoding and storage of memory within the mammalian hippocampus. Long-term potentiation was first described by Tim Bliss and Terje Lømo in 1973 in the rabbit dentate gyrus (1), and although a form of heterosynaptic LTD was described in 1977 (2), most neuroscientists are more familiar with the homosynaptic LTD first described by Serena Dudek and Mark Bear (3). In the intervening years there has been an enormous amount of work devoted to these two forms of synaptic plasticity. In fact, if one types “long-term potentiation” or “long-term depression” into PubMed, the search engine returns >12,000 results for long-term potentiation and >3000 for long-term depression at the time of writing this review. And, despite the renaissance period of neuro-methods and neuro-technology that we are now experiencing, many questions regarding LTP/LTD remain. Although recent advancements in cellular imaging have provided us with a glimpse into the behavior of single spines (e.g., Nair et al. (4)), we still lack an appreciation for how individual synapses influence neuronal output during plasticity.

In this issue of the *Biophysical Journal*, Migliore et al. (5) begin to address

this knowledge gap using the NEURON simulation environment and a previously described high-fidelity, three-dimensional model of a hippocampal CA1 pyramidal neuron (6). In this work, the model has been modified to include dynamic synapses such that presynaptic events produce a postsynaptic depolarization. Postsynaptic depolarization is coupled to terms N_P and N_D , which regulate the net postsynaptic response. The behavior of N_P and N_D is described by a pair of differential equations that act more or less as a bistable switch with two conditions (ground and high), with the high state leading to the induction and maintenance of LTP (N_P) or LTD (N_D).

In their initial simulations, the authors validated the model using a θ -burst stimulation protocol to induce LTP (TBS-LTP; four presynaptic pulses at 100 Hz repeated at 200-ms intervals) and LTD (LFD-LTD; two pulses at 100 Hz repeated at 10-s intervals). The authors also demonstrated that all of the synapses could exhibit depotentiation (reversal of previously induced LTP). The spatial control afforded by the model also allowed the authors to examine another type of LTP, known as heterosynaptic LTP. In this form of LTP, individual synapses could be potentiated even though they were not activated as long as they were within $\sim 70 \mu\text{m}$ of an adjacent activated synapse. In all cases, the model performed to previously obtained experimental results.

After validating the model, the authors set out to systematically determine to what extent the initial state of individual synapses might influence the induction of LTP or LTD. In the first set of simulations, the authors demonstrate that varying the starting weight of the synapses in a uniform manner can have profound effects on the resulting plasticity. As might be expected, the simulations indicate that maximal LTP could be induced for most synapses that had not previously been potentiated (i.e., $N_P = 0$). Conversely, synapses that had previ-

ously been potentiated could not be potentiated regardless of their peak conductance values. The picture for LTD appears to be more complicated (and interesting). When LTD is induced from the ground state ($N_D = 0$), only a subset of synapses whose peak conductance was between 0.6 and 0.11 nS exhibited any LTD. In contrast, when LTD was induced from the potentiated state, almost all synapses exhibited LTD, regardless of their peak conductance, with synapses in the 0.6–0.11 nS range exhibiting the greatest LTD. These results suggest that in a real neuron, the probability of inducing LTP/LTD, and the amplitude of the resulting plasticity would depend not only on the previous experience of the synapse but also its peak conductance.

To get at this issue, Migliore et al. (5) carried out simulations using synapses with randomly assigned peak conductances and same LTP and LTD induction protocols starting at ground state. While the LTP protocol resulted in LTP across all synapses regardless of peak conductance, the LTD induction protocol resulted in LTD at some synapses (0.7–0.11 nS), LTP at others (0.11–0.13 nS), and no change in a third population of synapses (0.5–0.7 nS). In addition, the authors examined the impact of peak conductance on LTD induced by low-frequency stimulation (0.5–7 Hz) induction protocols of varying peak conductances from different initialization states (ground, potentiated, and depressed). Starting from ground state, synapses exhibited a very narrow band of peak conductances and stimulation frequencies capable of producing LTD with the larger conductances producing LTP at the higher stimulation ranges (3–7 Hz). This band of LTD was wider when synapses started from a potentiated state and was flanked by synapses that exhibited little plasticity regardless of the

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stimulation frequency or their peak conduction. Finally, synapses that started from a depressed state ($N_D = \text{max}$) not only failed to exhibit LTD but typically exhibited LTP, which in some cases was quite robust.

The data presented by Migliore et al. (5) provide valuable insight into potential rules regarding the plasticity at individual synapses, which would be obscured in most ex vivo experiments that utilize acutely prepared hippocampal slices to investigate LTP and LTD. While it is reasonable to assume that the synapses that collectively give rise to the excitatory postsynaptic potential measure at the soma in these experiments would have a variety of peak conductances, as of this writing it is impossible to know the starting state of these synapses. The authors suggest that one solution might be to precondition the synapses such that synapses could be in a favorable state before the induction of plasticity. Although the concept of preconditioning remains to be tested rigorously, there is some evidence that simply altering stimula-

tion frequencies during repetitive stimulation at low frequency can induce a form of homeostatic synaptic plasticity. In this case, shifting from a very low frequency (0.0033 Hz) to a higher frequency (0.05 Hz) produces an LTD-like phenomenon, while shifting from a higher frequency (0.05 Hz) to a lower frequency (0.0033 Hz) induces an LTP-like phenomenon ((7), M. A. Sutton, University of Michigan, personal communication, 2014). Is it possible that the ground state of all of the individual synapses might be reset and altered by this ultra-low-frequency stimulation? And does this sort of situation exist in vivo? As of this writing, these and many other questions regarding synaptic plasticity remain unknown, but the article by Migliore et al. (5) goes a long way toward defining the possibilities and parameter space.

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